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(54) Title: COMPOSITIONS COMPRISING MMP7 MODULATORS FOR THE TREATMENT OF CHRONIC PAIN

(57) Abstract: The invention discloses MMP7 as a suitable target for the development of new therapeutics to treat or ameliorate chronic pain. The invention relates to methods to treat and/or ameliorate chronic pain and pharmaceutical compositions therefor comprising modulators with inhibitory effect on MMP7 enzyme activity and/or MMP7 gene expression. The invention also relates to a method to identify compounds with therapeutic usefulness to treat chronic pain, comprising identifying compounds that can inhibit MMP7 activity and/or gene expression which can also reverse the pathological effects of chronic pain *in vivo*.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03643

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61K39/395 A61K31/7088 A61P25/02 C12Q1/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data, CANCERLIT, SCISEARCH, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/06213 A (BARRETT STEPHEN DOUGLAS ;WARMUS JOSEPH SCOTT (US); WARNER LAMBERT) 24 January 2002 (2002-01-24) page 1, line 4 - line 6 page 86, line 6 - line 25 example 246 -----	1-4,6, 13,14, 16,20
X	US 6 037 361 A (O'BRIEN PATRICK MICHAEL ET AL) 14 March 2000 (2000-03-14) column 6, line 16 - line 25 column 14, line 31 - line 32 scheme 1, compounds 18-23, 30-35, 42-53 examples 17,18 claims 14,29 ----- -----	1-4,6, 13,14, 16,20

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

14 July 2003

Date of mailing of the international search report

30.12.03

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03643

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/092244 A (FRIDMAN RAFAEL ;MOBASHERY SHAHRIAR (US); UNIV WAYNE STATE (US)) 6 December 2001 (2001-12-06) page 5, line 1 page 17, line 29 - line 31 page 18, line 29 - page 19, line 5 claims 42,43 -----	13,14
X	WO 01/082911 A (XILINAS MICHEL ;GEROLYMATOS P N SA (GR)) 8 November 2001 (2001-11-08) page 19, line 26 - page 20, line 21 example 4 -----	13,14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/03643

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-4,6,7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: **1-4,6,13,14,16,20 (all in part)** because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4,6,7,13,14,16,17,20,21 (1-4,6,13,14,16,20 partially)

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,6,13,14,16,20 (all in part)

Present claims 1-3,13 relate to a compound defined by reference to a desirable characteristic or property, namely the capability of "modulating" matrilysin (MMP7). Due to its broad meaning, this term is considered to be vague and unclear in the sense of Article 6 PCT, and has thus been limited to MMP7 inhibition as indicated on p.7 of the description and in claims 4 and 14. However, since this expression covers all compounds having this property, and thus relates to an extremely large number of possible compounds, a complete search of this expression is impossible.

As for claims 6, 16 and 20, the term "hydroxamic acid derivatives" still encompasses an extremely large number of possible compounds, rendering a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been limited to the term "hydroxamic" and to the specific compound disclosed in claim 7.

In addition, the applicant's attention is drawn to the fact that some compounds may be already known to treat the diseases/disorders claimed by the applicant but are as yet not identified as MMP7 inhibitors.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4,6,7,13,14,16,17,20,21 (1-4,6,13,14,16,20 partially)

Pharmaceutical compositions comprising a MMP7 inhibitor for the treatment of chronic pain, whereby the MMP7 inhibitor is a hydroxamic acid derivative

2. claims: 1-3,5,8,13,15,18 (1-3,5,13,15 partially)

Pharmaceutical compositions comprising a MMP7 inhibitor for the treatment of chronic pain, whereby the MMP7 inhibitor inhibits MMP7 gene expression and is selected from antisense oligonucleotides, triple helix DNA, ribozymes, RNA aptamers or double stranded RNA

3. claims: 1-4,9,13,14,19 (1-4,13,14 partially)

Pharmaceutical compositions comprising a MMP7 inhibitor for the treatment of chronic pain, whereby the MMP7 inhibitor comprises one or more antibodies to MMP7 or fragments thereof

4. claims: 10-12

Method of identifying the ability of compounds to inhibit MMP7 enzyme activity or MMP7 gene expression

5. claims: 22-24

Diagnostic kit for detecting mRNA levels and/or protein levels of MMP7 in a biological sample and method of diagnosing and treating subjects suitable for chronic pain treatment with MMP7 inhibitors

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/03643

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